South African Medical Journal
Suid-Afrikaanse Tydskrif vir Geneeskunde

Vol. 24, No. 8. Cape Town, 25 February 1950 Weekly 2s

STUDIES IN AMOEBIASIS

THE EFFECT OF ANTI-BACTERIAL DRUGS

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In previous papers[1, 2, 3] covering our earlier experiences at King-Edward VIII Hospital we recorded the results of the treatment of amoebiasis by a number of drugs used singly and in combination. A notable feature of the previous series was the synergistic effect of the addition of the anti-bacterial drugs to the anti-amoebic drugs. This had confirmed the findings of Hargreaves[4] and others. We wished, however, to find out how much of this effect was due to anti-bacterial drugs alone without the addition of the amoebicides.

A small pilot series was first undertaken using penicillin and sulphasuxidine together. The dosage was six million units of penicillin and 300 gm. of sulphasuxidine equally divided over 21 days. The customary sigmoidoscopy and the examination of stools and scrapings were done at the end of 10 days, 20 days and 27 days. At the end of 10 days all the ulcers were clean and either healed or healing, and in not one of the 11 cases could an amoeba be found, either in stools or scrapings. At 27 days, i.e. after seven days without treatment after completion of the course, nine of the cases were soundly healed and symptom free. Two cases were symptom free but still had an open ulcer which, although clean, necessitated classification as 'probable failures'. No cases showed amoebae in any form. Two of these cases were followed up for a further three months and showed no relapse.

The success of this admittedly small series was so great that we embarked on larger series using the two drugs separately.

THE EFFECT OF SULFASUXIDINE ALONE

This series comprised of 57 cases. The dosage employed was 30 tablets *stat.*, then six tablets five times a day given 4-hourly over 20 days. It is to be noted that in a week we gave 120 gm., nearly double that of Hargreaves' original course, and nearly half as much again as his later recommendation of 87 gm. in seven days. Moreover, it was given continuously for three weeks, instead of for seven days as in Hargreaves' cases. Results were assessed by serial sigmoidoscopy and examination of scrapings at 10, 20 and 27 days, i.e. seven days after the completion of the course and without further treatment.

Where there was a deterioration in general health, patients were taken off the series for more orthodox treatment. One such case was transferred on the sixth day and another on the tenth day. We took 10 absolute failures and one probable failure off the series at 20 days for more conventional treatment. We did not know at this time that two out of seven absolute failures and seven out of 13 probable failures found at 20 days and allowed to proceed on the series would subsequently and spontaneously become successes. One patient discharged himself from hospital at 20 days even though we regarded him as an absolute failure. These defections explain the gradual diminution in numbers as the course of treatment progressed. Results of treatment are tabulated in Table I.

It will be seen that sulphasuxidine has a profound effect on amoebic dysentery both in promoting healing of ulcers and in causing disappearance of amoebae from scrapings. These effects were noticeable even at the second sigmoidoscopy 10 days after treatment had commenced. At this early stage, many of the ulcers were already healed, and indeed in nine cases healing was complete in the visible part of the bowel. In other cases where open ulcers were seen at the tenth day, most of them were clean and lacking the exudate which had been present before.

Several points are worthy of note. During the course of treatment there is a steady increase in the number of successes and an equally steady decline in both

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TABLE I

The Use of Sulphasuxidine in the Treatment of Acute Amoebic Dysentry (Original Number 57)

10 *Days*	56 *Cases*	*Current Rate*	*Cumulative Rate*
Absolute Failures	21 (22*)	37·5% of 56	38·6% of 57
Probable Failures	26	46·5%	45·6%
Successes	9	16·0%	15·8%
20 *Days*	55 *Cases*		
Absolute Failures	18 (20*)	32·7% of 55	36·5% of 57
Probable Failures	15	27·2%	26·5%
Successes	22	40·0%	38·5%
27 *Days*	42 *Cases*		
Absolute Failures	3 (18*)	7·2% of 42	31·5% of 57
Probable Failures	8	19·0%	14·0%
Successes	31	74·0%	54·5%

The figures in brackets (*) are obtained by assuming that all absolute failures eliminated would remain so subsequently and adding to them the absolute failures observed on the given date.

categories of failures. In particular, it should be noticed that at 10 days after the start of treatment only 37.5% still had amoebae in scrapings and stools. In other words, 62.5% or nearly two thirds, had been rendered free of symptoms and amoebae in only 10 days. This is a matter of first importance and clearly demonstrates the danger of giving sulphasuxidine or other 'sulpha' drugs to patients suffering from undiagnosed dysentery. The indiscriminate use of sulpha drugs in the acute phase of dysentery before a firm diagnosis has been made, will result in two-thirds of all cases of amoebiasis being suppressed.

It is worth comparing the figures recorded at 20 days treatment with sulphasuxidine with the series of 50 cases treated with emetine by injection. Under this treatment successes were 50%, probable failures 22%, and absolute failures 28%. It will at once be apparent that there is very little therapeutic difference between the immediate effects of sulphasuxidine and those of emetine, which has generally been regarded as the most effective anti-amoebic agent at our disposal.

Between the 20th and 27th days none of these patients received any treatment. Yet the successes increased by nine cases. Two out of seven absolute failures and seven out of 13 probable failures became successes. The overall figures at 27 days are unfortunately misleading and cannot be given accurately. It is certain that the figure of 7.2% of 42 patients available at that time is too low a figure for the real number of absolute failures. On the other hand, the higher figure of 31.5% of the 57 cases originally placed on the series is too high an absolute failure rate. This latter figure was arrived at by assuming that all the eliminated cases, including the 11 which were eliminated at 20 days, would have been absolute failures on the 27th day. But we know that two out of seven absolute failures at 20 days became successes at 27 days. The figures given present the worst possible result achievable with sulphasuxidine, but even so they show a continuation in the upward trend of successes and downward trend of absolute failures.

The improvement between the 20th and 27th day when no treatment was given, both in individual cases and in the statistical returns, show that a considerable lapse of time is required for complete healing to take place. It confirms the impression which we have gained during hundreds of therapeutic trials with other drugs. Although some cases heal very rapidly, even by the tenth day, it is probable that assessment at 20 days is too early, and a further quota may be expected to heal in the next seven to 10 days.

THE EFFECT OF PENICILLIN ALONE

This series comprised 55 cases, each of which was treated with 300,000 units of procaine penicillin in oil daily for 20 days. As with sulphasuxidine, results were assessed at 10, 20 and 27 days, i.e. seven days after the completion of the course without further treatment.

One very ill patient was taken off the series and given orthodox treatment after only three days of penicillin. He died two days later. He is included as an absolute failure in all subsequent assessments, thus making the table correspond with that for sulphasuxidine.

One patient accidentally overlooked at 10 days was not sigmoidoscoped on this day and reduces the 10-day number by one. He was sigmoidoscoped and included on both subsequent examination days.

At 20 days, 10 patients were given more orthodox treatment as it was felt that their condition, though by no means serious, did not justify their retention on the series for another week without further treatment. This explains the diminution in numbers at 27 days. Of these 10, nine were absolute failures and one a probable failure.

These results are very similar to those obtained with sulphasuxidine alone. All that has been said in the preceding paragraphs about the effects of sulphasuxidine applies equally to the effects of penicillin and needs no repetition. There was the same steady tendency to cure with the passage of time, and the same cleansing, the healing of ulcers and the same increase in the number of successes when treatment was withdrawn at the 20th day. From statistical analysis it seems that there is no material difference between the effects of the two drugs.

TABLE II

The Use of Pencillin in the Treatment of Acute Amoebic Dysentry (Original Number 55)

	10 *Days*	53 *Cases*	*Current Rate*	*Cumulative Rate*
Absolute Failures	... ...	25 (26*)	47·25% of 53	48·25% of 54
Probable Failures	... ...	16	30·25%	29· 5%
Successes ...	... ...	12	22·5%	22·25%
	20 *Days*	52 *Cases*		
Absolute Failures	... ...	19 (22*)	36·5% of 52	40·00% of 55
Probable Failures	... ...	12	23·2%	21·75%
Successes ...	... ...	21	40·5%	38·25%
	27 *Days*	42 *Cases*		
Absolute Failures	... ...	8 (20*)	19·0% of 42	36·5 % of 55
Probable Failures	... ...	9 (10*)	21·5%	18·25%
Successes ...	... ...	25	59·5%	45·25%

The figures in brackets (*) are obtained by assuming that all cases eliminated as absolute failures remained absolute failures subsequently and that the one case eliminated as a probable failure subsequently remained a probable failure.

Fifteen cases which remained failures on penicillin were then treated with sulphasuxidine. Only four cases were not improved. Of the 11 cases improved, seven were assessed as cures. Five of these were cured after only seven days of sulphasuxidine and a further two after 14 days. One case returned after a further 14 days and was still apparently cured. One case assessed as a cure at seven days after starting sulphasuxidine returned to hospital 14 days later and died of a fulminating relapse of amoebiasis. This case was peculiar for ulcers seen at 20 days of treatment with penicillin had healed seven days later. But at this time the normal mucosa of the lower bowel was covered with bloody mucus presumably coming from open ulcers at a higher level. He was assessed as a failure but a week later after sulphasuxidine was classed as a success. His subsequent death confirms the persistence of active lesions in the upper colon.

A CONTROL GROUP

In order to eliminate the possibility of spontaneous cure it is necessary to observe a series of cases without treatment. For obvious reasons this is difficult to obtain. However, when we were asked officially to conduct trials of certain compounds which were being widely advertised without scientific background an opportunity arose for us to collect a certain number of additional figures.[5] The two compounds—chlorobexol and 260 D—were so poor that it can be assumed that they had no curative action. They may well be lumped together with the series which received no treatment at all. The results of this series are reported in Table III

It will be seen that a very large proportion of cases had to be removed from the series owing to the serious deterioration in their clinical condition. Nevertheless three cases were classed as 'successes'. This confirms

TABLE III

The Use of Chlorobexol and 260 D in the Treatment of Acute Amoebic Dysentry (Original Number 50)

	7 *Days*	50 *Cases*	*Current Rate*	*Cumulative Rate*
Absolute Failures	... ...	41	82·0% of 50	82·0% of 50
Probable Failures	... ...	9	18·0%	18·0%
Successes ...	... ...	0	0	0
	14 *Days*	36 *Cases*		
Absolute Failures	... ...	22 (36*)	61·0% of 36	72·0% of 50
Probable Failures	... ...	14	39·0%	28·0%
Successes ...	... ...	0	0	0
	21 *Days*	22 *Cases*		
Absolute Failures	... ...	16 (44*)	72·7% of 22	88·0% of 50
Probable Failures	... ...	5	22·7%	10·0%
Successes ...	... ...	1	4·5%	2·0%
	28 *Days*	8 *Cases*		
Absolute Failures	... ...	3 (45*)	37·5% of 8	90·0% of 50
Probable Failures	... ...	2	25·0%	4·0%
Successes ...	... ...	3	37·5%	6·0%

the observation of Coxon[6] who reported one success in nine cases treated only with placebos.

DISCUSSION

It is apparent from our results that anti-bacterial drugs by themselves are capable of modifying considerably the course of the acute amoebiasis which we see in Africans. These drugs are, in the enormous doses we have used, quite as capable of 'success' as in emetine. This fact must cause us to modify our views of the condition and the relative importance of the various factors concerned. It is well known that penicillin and sulphasuxidine have little or no effect on the amoebae *in vitro* except in so far as they modify the associated bacterial flora. In fact, in the technique of culturing amoebae in the absence of living bacteria, penicillin is used to restrain the growth of the only bacterium present.[7] Apparently in our series we have so modified the bacterial flora that it no longer constitutes the nidus hitherto so favourable to the amoeba. The nature of this change in bacterial flora will have to be determined by further study. As it involves the organisms normally considered non-pathogenic, it is likely to be protracted.

Other workers, notably Hargreaves,[4] Priest,[8] Willmore,[9] and Parkinson[10] have found that the use of the anti-bacterial drugs improved the condition of the patient but did not necessarily remove the amoebae. Parkinson found that the amoebae were likely to disappear and therefore deprecated the use of sulphonamides before the establishment of the diagnosis. None of these authors used the drugs in the high concentrations reported here and it must be emphasized that in carrying out these experiments we were more concerned with establishing the effect of the anti-bacterial drugs rather than providing a new form of therapy. It is obvious that there is a third party concerned in the host-amoeba relationship and that this organism or series of organisms is sometimes susceptible to drugs such as sulphasuxidine and penicillin. The fact that sulphasuxidine improved some cases which had failed on penicillin alone rather indicates that the third party may be one or other of a series of different micro-organisms. Further understanding of this point may lead in the future to a knowledge of what starts the invasive process of amoebiasis.

Finally we would emphasize again that in this paper we are not suggesting a new form of therapy. In fact we deprecate its use in all cases other than those showing the ulcerative form of the disease.

SUMMARY

Penicillin alone and sulphasuxidine alone are in a high proportion of cases capable of 'success' in the treatment of acute ulcerative amoebic dysentery.

Simultaneous use of the two drugs results in a greater proportion of cures.

The danger of masking the diagnosis of amoebiasis by the indiscriminate use of sulphonamides is stressed.

It is suggested that the anti-bacterial drugs exhibit their anti-amoebic action by the destruction of organisms symbiotic to the amoeba.

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ABSTRACTS

Acrokeratosis Verruciforme (*Acroératose Verruciforme*). Costa, O. G. and Oliveira Morais, F. (1949): Annal. Dermatol. Syphiligraph., **9,** 525.

A description with good illustrations of the first case of this rare naevoid condition to be discovered in South America. Lesions of finger pulp as demonstrated by fingerprinting are described for the first time.

Diffuse Lepra. M. E. Obermeyer, S. C. Bonar and R. Rosenquist (1949): J. Invest. Derm., **12,** 243.

Diffuse lepra was first described by R. Lucio in 1851 under the names of 'spotted' or 'Lazarine' lepra. It was again identified in 1937 by F. Latapí and co-workers who believe it to be an exclusively Mexican disease.

Diffuse Lepra has two special features; diffuse infiltration of the skin of the whole body and a peculiar reaction, 'Lucio's phenomenon' or erythma necroticans. The first signs are often anidrosis, numbness of extremities and slowly progressive loss of eyelashes and eyebrows. Nodules are not produced but the skin is diffusely infiltrated and, although appearing normal on inspection, gives an abnormal reaction to histamine. *Mycobacterim leprae* can usually be obtained by the scraped incision method from any region of the skin. In some cases there is chronic diffuse swelling of the face, hands and legs. There are often widespread small telangiectases particularly on face and trunk.

The unique lesions appear after 3-4 years, few at first, numerous later. The lesions are irregularly shaped, tender, painful, erythematous, slightly infiltrated macules, 0.5 to 1 c.m. in diameter. They appear first on the legs and, to a lesser extent on the arms, only involving face and trunk much later. The development and involution of individual macules are uniform and rapid, the cycle taking two weeks. The lesions darken and become purpuric in three to four days; central necrosis develops and an eschar forms and falls off in a few days leaving a superficial, sharply circumscribed atrophic scar. At times there is ulceration with delay in healing and the production of a deep scar. Lesions at all stages can be seen at the same time.

Many of the manifestations commonly encountered in ordinary lepromatous lepra are seen in the diffuse type; but it is noteworthy that ocular involvement and formation of cutaneous nodules are not observed. Untreated, the disease terminates in about eight years.

The Wassermann and Kahn tests are always positive and the sedimentation rate is extraordinarily high. The reaction to the conventional lepromin (Mitsuda) test is negative. The use of sulfones has improved the prognosis. A case in an American of Mexican descent is described.

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VAN DIE REDAKSIE

HUIDIGE OPVATTINGS OOR DIE GENESENDE BEHANDELING VAN SIFILIS

Die huidige eeu was 'n tydperk van snelle vordering op die gebied van die behandeling en beheer van sifilis. Sedert Ehrlich se ontdekking van salvarsan in 1909, is die weg van vooruitgang met baie verwagtings en teleurstellings besaai, maar daarteenoor is ook aansienlike vordering gemaak.

In die penisillinkuur het ons die veiligste en eenvoudigste vorm van behandeling wat tot dusver ontwerp is, maar die gemak waarmee dit toegepas kan word, mag op sigself die gevaar uitmaak. Aangesien genesing so gou plaasvind, is die eertydse pasiënt geneig om weer die risiko van besmetting te loop. Dit mag die verklaring wees vir die vermeerdering in die aantal sifilisgevalle wat in sekere oorde opgemerk is.

Evan W. Thomas, Direkteur van die *Rapid Treatment Centre*, Bellevue-hospitaal, New York, gee in sy boek[1] wat onlangs verskyn het die uitslae van 12,000 gevalle van sifilis wat met verskillende reekse toedienings van penisillin, alleen of saam met kort reekse toedienings van fenarseen en bismut, behandel is. Hierdie syfers bring aan die lig dat die mislukkingsyfer vir die geheel byna 20% is, maar aangesien dit moeilik is om te onderskei tussen hervattings en herbesemettings skat hy die ‚juiste' mislukkingsyfer op naasteby 10%. Dr. C. K. O'Malley se uitstekende en leersame verslag, in hierdie uitgawe, van 365 gevalle van sifilis in die vroeë stadium, wat in die Kaapstadse Munisipale Klinieke behandel is, bevestig hierdie syfers.

Die ou ‚roetine'-behandeling met reekse toedienings van arseen en bismut oor 'n tydperk van nege tot 18 maande lewer beter resultate wanneer dit behoorlik uitgevoer word. Thomas het egter gevind dat minder as 20% van die kliniese gevalle in New York die ‚routine'-behandeling voltooi het. Toksiese reaksies het taamlik gereeld voorgekom en was soms gevaarlik.

1. *Syphilis: Its Course and Management* (1949), New York: Die Macmillan My.

EDITORIAL

CURRENT CONCEPTS OF ANTI-SYPHILITIC THERAPY

The present century has been a period of rapid advancement in the treatment and control of syphilis. From Ehrlich's discovery of salvarsan in 1909 the path of progress has been marked by many hopes and disappointments, but, on the other hand, many real advances have been made.

In penicillin therapy we have the safest and simplest treatment so far devised; but the very ease of its administration may in itself constitute the danger. As the cure is so rapid, the erstwhile patient is disposed to take the risk of infection again. This may account for the increase in the cases of syphilis noted in certain quarters.

Evan W. Thomas, Director of the Rapid Treatment Centre, Bellevue Hospital, New York, in his recent publication[1], gives the results of 12,000 cases of syphilis, treated with various schedules of penicillin therapy given alone or combined with short courses of phenarsine and bismuth. An overall failure rate of nearly 20% is revealed by these figures, but as relapses and re-infections are difficult to distinguish he estimates that the ' true ' failure rate is nearer 10%. Dr. C. K. O'Malley's excellent and informative report in this issue, on 365 cases of early syphilis treated in the Municipal Clinics in Cape Town, confirms these figures.

The older ' routine ' treatment with courses of arsenic and bismuth given during nine to 18 months, when properly carried out, gave better results. Thomas found, however, that less than 20% of his clinic cases in New York completed this ' routine ' treatment. Toxic reactions were not infrequent and were sometimes dangerous. Obviously, it will be a great achievement

1. *Syphilis: Its Course and Management.* (1949). New York: The Macmillan Co.

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Dit sal klaarblyklik 'n groot prestasie wees indien 'n intensiewe genesende reeks toedienings uitgewerk kan word wat die toediening van penisillin wat vry van giftigheid is, vir slegs agt tot 15 dae vereis.

Die opvolging van gevalle van vroeë sifilis is van die uiterste belang. Thomas doen aan die hand dat dit gedurende die eerste jaar uit maandelikse kwantitatiewe bloedtoetse bestaan; die tweede jaar uit toetse elke twee tot drie maande en daarna toetse wat lewenslank jaarliks tesame met kliniese ondersoeke en ondersoeke van die rugmurgvloeistof gedoen word. Hy meld nie hoeveel gevalle nie die waarnemingstydperk voltooi het nie. Dr. O'Malley se uitslae toon dat van sy 365 gevalle van vroeë sifilis, minder as 50% hulself na drie maande aangemeld het, minder as 40% na ses maande en minder as 25% na een jaar. Aansienlik meer vroue as mans het hulle na 12 maande aangemeld, maar van die 12 gevalle waar behandeling misluk het, was nege vroue.

Dr. O'Malley moet geluk gewens word omdat hy ses maande na die voltooiing van die behandeling, in meer as 20% van sy gevalle ondersoeke van die rugmurgvloeistof verkry het, waarvan slegs een reaksie twyfelagtig was en die ander almal normaal.

Thomas en andere het 'n interessante waarneming gedoen wat van aansienlike belang is vir 'n begrip van sifilis. Baie hervattings en herbesmettings word na die moderne kort intensiewe reekse toedienings aangemeld. Thomas glo dat gevalle wat nie behandel word nie geleidelik 'n ‚toestand van immuniteit' of ‚weerstandbiedende toestand' teen aansteeklike sifilissere ontwikkel en dat die toestand in feitlik alle gevalle aan die end van twee jaar na besmetting volledig is. Behandeling teen sifilis, wanneer dit in die vroeë stadiums van besmetting toegepas word, bemoeilik die ontwikkeling van die weerstandbiedende toestand. Gevolglik kan pasiënte na mislukte behandeling hervattings met aansteeklike sere hê en na suksesvolle behandeling kan pasiënte herbesmet word deur die ontwikkeling van primêre of sekondêre sere. Indien die ‚weerstandbiedende toestand' ten volle ontwikkel het, sou sulke sere nie voorgekom het nie. Hierdie opvatting van relatiewe immuniteit gepaard met die snelheid van genesing deur penisillin, mag die feit verklaar dat 'n tweede aanval van sifilis deesdae betreklik dikwels voorkom.

Juiste diagnose is nog noodsaaklik. Die aanwesigheid van *Treponema pallidum* moet bewys word of verskeie positiewe serologiese reaksies moet verkry word voordat die behandeling begin word. Daar moet streng by erkende behandelingsreekse gehou word aangesien in gedagte gehou moet word dat die kragtigheidsbepaling van penisillin nog nie voltooi is nie alhoewel, volgens die getuienis wat op die oomblik beskikbaar is, dit wil voorkom of 'n totale dosering van 4.5 miljoen eenhede oor 'n tydperk van agt tot 15 dae toegedien, beskou moet word as die minimum wat aanneemlik is. Daar moet nog gesien word of die nuwer preparate van prokaïne en penisillin in olie saam met aluminium monostearaat as die verkieslikste vir genesende behandeling beskou sal word.

Intussen moet verkwisting van hierdie kosbare geneesmiddel vermy word en daar moet onthou word dat die uiteindelike beheer van sifilis nog afhang van spoedige diagnose, toereikende behandeling en lang waarneming.

if an intensive, curative schedule requiring only eight to 15 days of toxic-free penicillin is devised.

The follow-up of treated cases of early syphilis is of the utmost importance. Thomas advises that this should consist of monthly quantitative blood tests during the first year; of tests taken every two to three months during the second year, and thereafter tests taken yearly for life, together with clinical examinations and examinations of the cerebrospinal fluid. He does not report the number of cases who failed to complete a two-year period of observation. Dr. O'Malley's results show that of his 365 cases of early syphilis, less than 50% reported at the end of three months, less than 40% at the end of six months, and less than 25% at the end of one year. Considerably more females than males reported at the end of 12 months, but of 12 treatment failures, nine were females.

Dr. O'Malley is to be congratulated on having obtained spinal fluid examinations six months after the completion of treatment, in more than 20% of his cases, one doubtful reaction only being observed, all others being normal.

Thomas and others have made an interesting observation which is of considerable importance in the understanding of syphilis. Many more relapses and re-infections are being reported following the modern short intensive treatment schedules. Thomas believes that an 'immunity' or 'refractory state' to early infectious syphilitic lesions develops gradually in untreated cases and is complete in almost all at the end of the second year after infection. Anti-syphilitic treatment, given in the early stages of infection, interferes with the development of this refractory state. As a result, following unsuccessful therapy, patients may relapse with infectious lesions, and following successful therapy, patients may be re-infected with the development of primary or secondary lesions. Had the 'refractory state' been fully established, such lesions would not be manifest. This concept of relative immunity, coupled with the speed of cure by penicillin, may account for the fact that nowadays second attacks of syphilis are a relatively common occurrence.

Accurate diagnosis is still essential. The *Treponema pallidum* must be demonstrated or several positive serological reactions obtained before treatment is commenced. Accepted schedules of treatment must be rigidly adhered to, it being remembered that the evaluation of penicillin has not yet been completed, though the evidence before us to-day suggests that a total dosage of somewhere around 4.5 million units, given over a period of eight to 15 days, should be considered the minimum acceptable. It remains to be seen whether the newer preparations of procaine penicillin in oil combined with aluminium monostearate will establish themselves as the therapy of choice.

Meanwhile, wastage of this precious drug must be avoided and it should be remembered that the ultimate control of syphilis still depends on early diagnosis, adequate treatment and long observation.

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PENICILLIN IN EARLY SYPHILIS

RESULTS OBTAINED IN 365 CASES

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The proper evaluation of penicillin in the treatment of syphilis is a laborious undertaking. It can only be done by collecting all available statistical data, which must then be sifted, appraised and, finally, either rejected as offering no suitable material or added to the common stock of knowledge. Medical literature abounds with reports on penicillin—treated cases of syphilis, so that even though the last word has not been said, we are in possession of some undisputed, fundamental facts. We know, e.g., that the toxicity of penicillin is low, that it is highly curative, but that there is a seemingly inevitable relapse rate when large numbers are treated, no matter what dosage scheme is employed.

The present report deals with the results obtained in treating early syphilis with varying dosages of penicillin, combined with an arsenical and bismuth. The patients concerned were admitted to the venereal disease wards of the City Hospital for Infectious Diseases, Cape Town. Only patients suffering from early syphilis were so treated. These cases fall under the following diagnostic headings:

S.1. Primary syphilis, *S. pallida* +, Wassermann negative.
S.2. Primary syphilis, *S. pallida* +, Wassermann positive.
S.3. Secondary syphilis, *S. pallida*, and/or Wassermann positive.

Table 1 shows the number of patients included in the investigation, arranged under these three diagnostic headings and classified according to sex and race.

TABLE 1

No. of Patients Investigated, Arranged According to Sex and Race

	Europeans	Non-Europeans	Totals
Males	94	110	204
Females ...	11	150	161
Totals ...	105	260	365

Table 1 includes patients only treated during the 12-month period July 1947 to July 1948. Before July 1947, penicillin alone was used in such cases but following Eagle's observation on rabbits[1] that a synergistic action existed between penicillin and arsenic, the combined use of these drugs was instituted. Eagle's findings held out the promise that the concomitant exhibition of arsenic and bismuth to patients receiving penicillin would greatly enhance the value of the latter. It is now known that this favourable outcome was not realized, that what happened in rabbit syphilis is not necessarily reproduced in human syphilis. What Eagle stated for mapharside was found to apply to bismuth.[2] It was decided to apply the principles established in experimental syphilis by these research workers to our cases. Each of our patients received, therefore, not only penicillin, but an arsenical and bismuth as well.

The general management of the patient was on the following lines: As soon as the diagnosis was established, either by dark-ground examination and/or a Wassermann test, treatment was begun. Aqueous penicillin was given by intramuscular injection at 3-hourly intervals for a period lasting from 7½ to 8 days. The great majority of the patients received crystalline penicillin G and no distinction is made in these tables between those patients receiving the drug in this form and those receiving the older preparations. Injections of an arseno-benzol were given on alternate days, i.e. every patient received 3-4 injections of a dose commensurate with body weight. The arsenical used was some member of the phenarsine group, either mapharside (P.D.Co.) or neo-halarsine (May Baker). Bismuth was administered as the salicylate suspended in oily medium, once or twice weekly. The total dosage of penicillin was determined according to the body weight and is here considered under three headings; less than 2 million units, between 2 and 3 million units, and between 3 and 4½ million units. Individual doses of arsenic and bismuth were also computed on the basis of body weight but these different doses are not dealt with specially in the tables. No further treatment was given after the patient left hospital.

The follow-up of patients consisted of inspection and serological tests at 3-monthly intervals. Patients were instructed to return three months after their discharge from hospital, when they were examined and questioned for any abnormal symptoms. A specimen of blood was taken for serological examination. Six months after treatment a complete examination of the spinal fluid, in addition to the usual blood tests, was carried out in all patients who agreed to have the test done. Refusal was rarely encountered, once contact was made with the patient. The fact that such a small number of our patients did have a spinal fluid examination is due more to defaulting than to their unwillingness to submit to a lumbar puncture. Those whose tests were completely negative at this period were urged to re-attend after a further six months' interval, i.e. twelve months after the cessation of anti-syphilitic

TABLE 2

No. of Patients Investigated Arranged According to Diagnosis, Race and Sex

Diagnosis	Males		Total	Females		Total	Totals Combined
	European	Coloured		European	Coloured		
S 1	28	10	38	1	1	2	40
S 2	28	19	47	—	10	10	57
S 3	38	81	119	10	139	149	268
Totals ...	94	110	204	11	150	161	365

treatment. Unfortunately, the number of patients reporting back grew smaller and smaller as time went on, so that it was decided to base statistical findings, for what they were worth, on a 12-month rather than a 2-year period. Two years' observation is desirable for a more exacting appraisal of any treatment schedule of syphilis. At the same time it is felt that the results of a 12-month survey are not valueless, inasmuch as the majority of treatment failures usually show up within this time period.

Quantitative tests, unfortunately, were not available, so that our figures are based on the results of qualitative tests only. If, during the observation period a Wassermann test was reported 'positive' the patient concerned was considered a failure and further treatment was instituted. The performance of quantitative Wassermann tests on large numbers of patients would naturally strain the resources of any laboratory engaged in routine Public Health work. No doubt the quantitative Wassermann is desirable, and indeed, almost indispensable for accurate appraisal. Its absence from our routine, however, does not invalidate the general findings which are based on the absolutes 'negative', 'positive' and 'doubtful'.

The usual tests were performed on the spinal fluid, that is, Wassermann test, cell count, protein and globulin estimations. Four cells per c.mm. was taken as the normal cell count. As a matter of fact the application of this standard was not once called into question, as all fluids examined were completely negative, with cell counts ranging from 1 to 3. Examination of the spinal fluid was carried out six months after the cessation of all treatment. In no single instance was the spinal fluid found to be other than completely normal in our series.

Table 3 sets out in detail the number of patients reporting at the third, sixth and twelfth months after treatment. It is a record of progressive failure to report for these periodical checks and illustrates the ever-present tendency to default once signs and symptoms of disease have responded favourably to treatment.

The better co-operation of female patients is apparent from these figures. The most unco-operative group is the non-European males. Every endeavour is made to bring about the re-attendance of the defaulting patient. In the case of females, a personal visit is made by a member of the nurse-visitor staff. These ladies have had a large experience in this kind of work and, in most cases, have already had professional contact with the patients they visit. After three unsuccessful visits no further action is taken. Since the patient cannot now be considered as infectious, no compulsory methods are adopted to enforce attendance. Males are not subjected to a personal visit either at their places of work or homes. Instead, a routine standard letter exhorting them, in their own interests, to report for observation is sent at intervals. The letter is so worded that the message it conveys is not apparent to anyone other than the person directly concerned. If three such letters produce no response, nothing more can be done and the patient is reluctantly written off as 'self discharged'. Adding to the 'defaulter' list is the large number of merchant seamen in transit through Cape Town. Once their treatment is finished and they leave hospital, all contact with them is lost and their records are of no value to an enquiry of this nature.

TABLE 3

Showing the No. of Patients Reporting for Periodical Observation Arranged According to Sex and Race

Sex	*Race*	*Original No. of Patients Treated*	*Patients Reporting at the Third Month*		*Patients Reporting at the Sixth Month*		*Submitted to C.S.F. Examination at Sixth Month*		*No. of Patients Reporting at the Twelfth Month*	
			No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Males	European	94	51	(54·26)	43	(45·74)	35	(37·23)	26	(27·65)
	Coloured	110	42	(38·18)	28	(25·45)	14	(12·72)	12	(10·90)
Females	European	11	9	(81·81)	7	(63·63)	4	(36·37)	5	(45·45)
	Coloured	150	77	(51·33)	58	(38·66)	23	(15·33)	43	(28·66)
Totals		365	179	(49·04)	136	(37·26)	76	(20·82)	86	(23·56)

The chief point of this investigation was to determine the effect of a particular schedule, i.e. a combination of penicillin, arsenic and bismuth given under hospital conditions. Tables 4, 5 and 6 show the results of the Wassermann test performed at the third, sixth and twelfth month recorded as positive (+), doubtful (±) and negative (−). For convenience, the total number in each of the diagnostic categories (syphilis 1, 2 and 3) as well as the number of defaulters (D) at the stated intervals, are listed. Also shown in these tables are the results of a complete examination of the cerebro-spinal fluid performed at the sixth month.

Of the original 365 patients only 179 (49.04%) reported for their serological check at the third month. Of this number 34 (18.99%) (Table 6) were still 'positive', 141 (78.77%) 'negative' and the remainder 'doubtful'. At the sixth month 141 (38.63%) reported, giving 13 (9.21%) 'positives' and 119 (84.39%) 'negatives'. At the twelfth month, out of the 86 patients who presented themselves, 8 (9.3%) gave positive reactions to the blood Wassermann test, 7 (8.13%) doubtful and 71 (82.55%) negatives. The seven 'doubtful' cases were re-checked by a Kahn test in addition to a repeated Wassermann test. The eight cases which gave a positive blood Wassermann reaction were regarded as failures and put on treatment.

It is worthy of note that the failure of these eight cases to respond favourably to treatment was not due to the fact that they received a smaller total dosage of penicillin. As a matter of fact, each member of this failure group received more than 3 million units. In no instance where a smaller dosage, based on body weight, was used, did a serological relapse occur amongst those who were observed at the twelfth month.

TABLE 4

Showing the Results of the Wassermann Test in Male Penicillin-Treated Cases at the Third, Sixth and Twelfth Month after the Cessation of Treatment as well as the Spinal Fluid Status at the Sixth Month

Diagnosis	*No. of Patients*	*Wassermann Status at 3 Months*				*Wassermann Status at 6 Months*				*Wassermann Status at 12 Months*				*Spinal Fluid Status at 6 Months*			
		+	±	−	D	+	±	−	D	+	±	−	D	+	±	−	D
S 1	38	0	0	20	8	0	0	15	23	0	0	8	30	0	0	16	22
S 2	47	2	2	18	35	0	3	13	31	1	0	6	40	0	0	8	39
S 3	119	5	0	47	67	1	1	37	80	1	0	22	96	0	1	27	91
Totals ...	204	7	2	85	110	1	4	65	134	2	0	36	166	0	1	51	152

TABLE 5

Showing the Results of the Wassermann Test in Female Penicillin-Treated Cases at the Third, Sixth and Twelfth Month after the Cessation of Treatment as well as the Spinal Fluid Status at the Sixth Month

Diagnosis	*No. of Patients*	*Wassermann Status at 3 Months*				*Wassermann Status at 6 Months*				*Wassermann Status at 12 Months*				*Spinal Fluid Status at 6 Months*			
		+	±	−	D	+	±	−	D	+	±	−	D	+	±	−	D
S 1	2	0	0	2	0	0	0	1	1	0	0	1	1	0	0	0	2
S 2	10	0	0	4	6	0	0	4	6	0	1	2	7	0	0	2	8
S 3	149	27	2	50	70	12	5	49	83	6	6	32	105	0	0	25	124
Totals ...	161	27	2	56	76	12	5	54	90	6	7	35	113	0	0	27	134

TABLE 6

Showing the Results of the Wassermann Test of both Sexes Combined in Penicillin-Treated Cases at the Third, Sixth and Twelfth Month after the Cessation of Treatment as well as the Spinal Fluid Status at the Sixth Month

Combined Totals (Male and Female)	*Wassermann Status at 3 Months*				*Wassermann Status at 6 Months*				*Wassermann Status at 12 Months*				*Spinal Fluid Status at 6 Months*			
	+	±	−	D	+	±	−	D	+	±	−	D	+	±	−	D
365	34	4	141	186	13	9	119	224	8	7	71	279	0	1	78	286

The results of the cerebrospinal fluid examinations are of special importance and interest. Of the 79 cases which had their fluids tested, 78 (98.73%) were completely negative. One gave a 'doubtful' reaction to the Wassermann test, but was negative in all other respects, i.e. the cell count, protein and globulin were all within normal limits. In general terms it can be said that following an adequate course of treatment the spinal fluid is unlikely to become positive if it is negative at the sixth month, unless a re-dissemination of spirochaetes can be surmised, e.g. in those cases which relapse either clinically or serologically.

Table 7 presents a detailed list of re-treatment cases following evidence of unsatisfactory response to the schedule under consideration. Some of these re-treatment cases were definite relapses, while others were cases of sero-resistance, i.e. their blood tests were positive at the beginning of treatment and remained so. Relapses may be of two kinds, serological and clinical. Most observers, quoted by Moore,[3] are agreed that serological relapse precedes clinical relapse. For its early detection monthly quantitative tests are desirable, though usually unobtainable, owing to the volume of routine work imposed on our laboratories.

TABLE 7

Showing the Sex, Diagnosis and Other Details of Retreatment Cases

Identification No.	*Sex*		*Diagnosis*	*Penicillin Dosage (M=1 million Units)*	*Time of Relapse (Month)*	*Remarks*
	Male	*Female*				
16810		F	3	+3M	9	Serological relapse, L.P. not done.
16596		F	3	+3M	11	Serological relapse, L.P. not done. Infant's Wassermann negative.
16247		F	3	+3M	10	Serological followed by clinical relapse. Spinal fluid normal.
16281		F	2	+3M	9	Serological relapse. Spinal fluid normal. Infant's blood negative.
16777		F	3	+3M	Sero-resistance	Wassermann remained +. L.P. not done.
22819	M		2	+3M	9	Serological relapse, L.P. not done.
7745	M		3	+3M	12	Serological relapse. Spinal fluid normal.
16355		F	3	+3M	Sero-resistance	Wassermann remained +. L.P. not done.
16767		F	3	+3M	12	Serological relapse, L.P. not done.
6412		F	3	−2M	Sero-resistance	Child 5 years old. L.P. not done.
6585		F	3	+3M	Sero-resistance	Wassermann remained +. L.P. not done.
23495	M		3	+3M	12	Serological relapse.

In all, there were 12 cases requiring re-treatment of our original number of 365. But of these 365, only 178 (48.76%) reported at the third month, 141 (38.63%) at the sixth and 86 (23.56%) at the twelfth month. Of the original 204 male cases included in the investigation, 38 reported at the twelfth month (Table 4), i.e. (18.62%) while of a total of 161 females, 48 reported for examination at the twelfth month (Table 5), a percentage of (29.8%). Of the 12 'failures', three were males, the rest females. There were four cases of sero-resistance, the remaining eight being cases of sero-relapse, one of which showed muco-cutaneous lesions following the detection of the positive blood status. Only one of the cases, a child aged five years, had a total penicillin dose of less than 2 million units. The others had doses of 3 million units, or more (but never exceeding 4.8 million). No case of sero-negative primary syphilis relapsed. One case of sero-positive primary syphilis did so; the remaining relapse cases were all in the secondary stage of syphilis when they came under treatment.

No mention is made in these tables of any reactions of a serious nature, as none such occurred. Headache, mild pyrexia and vomiting were noted in a few cases, but never of such a degree as to necessitate cessation of treatment. Arsenical injections were made on alternate days, and every patient received glucose and ascorbic acid tablets daily, during the stay in hospital.

DISCUSSION

The observations of Eagle and Magnusson in experimental syphilis, which led to their statements that penicillin and mapharside and penicillin and bismuth were synergistic in action, naturally gave birth to the hope that these encouraging results in animals could be reproduced in man. One was entitled to believe that, as a result of the discovery of the phenomenon of synergism, submaximal doses of either mapharside (or other arsenical drug) or bismuth, combined with penicillin, would give much better results than the employment of penicillin alone. The simultaneous administration of penicillin, arsenic and bismuth promised even better results. In the treatment results presented in the foregoing tables there are not many grounds for assuming that the quick and easy road for the eradication of syphilitic infection has been found.

Certain desiderata exist for the proper evaluation of any treatment schedule of syphilis. Such are:

1. The rigid adherence to the schedule under consideration.
2. Frequent, quantitative serological examinations of the blood by the Wassermann and other tests.
3. Prolonged post-treatment observation—at least for two years.

The first desideratum can, of course, be achieved, as it is under the control of the investigator. The other

two are dependent on extraneous factors, chiefly the co-operation of patients, and the availability of a laboratory service able to deal with large numbers of quantitative tests. Fortunately, when local conditions fall short of the requirements for careful research, skilled observers in other countries fill the gaps in our knowledge. Eagle, Mahoney, Magnusson, Moore and many others have built up successive levels in our knowledge of the pharmacology of penicillin in syphilitic infection. In his usual lucid style Moore,[3] in his brilliant monograph *Penicillin in Syphilis* summarizes and comments on the findings of these research workers in the U.S.A. The following comments are mainly based on material in Moore's book, where due acknowledgment is made to the particular individuals responsible for work which has laid the foundation of our present knowledge.

Dosage of Penicillin in Early Syphilis. Within certain limits the therapeutic effect of penicillin is proportional to the total dosage given. Thus, better results are obtained with 2,000,000 units than with a dosage total of 600,000 units; but after a certain dosage level has been obtained, doubling that dose does not produce correspondingly better results. We do not get half as many failures with a total of 10 million units as we got with 5 million. What really matters is the concentration of penicillin in the blood. There would seem to be no advantage in exceeding that optimum which kills the *Spirochaeta pallida.* McDermott (quoted by Moore) opines that a penicillin concentration of 0.078 unit per c.c. is 'well above' the effective level, and states that this level may be maintained during a period of 120 hours by giving 40,000 units 3-hourly for 10 days. As yet, however, neither the minimal effective level nor the optimal duration period has been ascertained with any degree of certainty. The result is that medical officers have no hard and fast rules of dosage to follow. But that is no justification for the variety of treatment schedules encountered in practice and apparently based more on individual whims and the mood of the moment than on soundly established principles. There are, nevertheless, some guiding rules. We know, e.g. that penicillin is most effective on organisms in the stage of active multiplication and, conversely, that its effect on organisms in the resting stage is much less. Theoretically, then, it should have its most successful sphere of action in early syphilis, and the earlier the stage of syphilis the greater are the chances of eradicating the infection altogether.

Recorded observations prove that numerous cases of primary syphilis have been radically cured by penicillin. But the dosage which achieved this happy result should not be relied upon to have a similar effect on cases of late syphilis, such as, e.g. gummatous skin ulcerations, or late bone syphilis. Indeed, it would be wise, in dealing with late syphilis, to regard penicillin as a powerful addition to our present armamentarium, rather than as an automatic agent of cure.

There is one important difference between the actions of the arseno-benzols and penicillin, which has been stressed by Eagle. A single dose of an arsenical has the same effect when given as one single injection as it has when given in multiple smaller doses at intervals. The trouble, of course, is that with the arsenicals the minimum curative dose is far greater than the maximum tolerated dose, so that safety demands a series of multiple injections. On the other hand, the therapeutic efficiency of penicillin is considerably augmented merely by dividing any given dosage into numerous small ones: 80 injections of 60,000 units are far more beneficial than 4,800,000 units given by intravenous drip as a continuous operation. Merely subdividing the necessary total dosage and thus spreading out the treatment period enhances the action of penicillin. In other words, if a certain result is achieved by administering 1 million units in 10 daily injections of 100,000 units each, less than a million would be necessary if smaller doses were given at shorter intervals.

Although, for obvious reasons, that concentration of penicillin in the serum, which is optimal in human syphilis, is not known for certain, animal experiments show that a concentration of 0.01 unit per c.c. temporarily inhibits the growth of *Spirochaeta pallida.* Some animals were cured of syphilis by a penicillin dosage giving a serum concentration so low that it could not be detected. The optimum dosage of penicillin in syphilis is the expression of the ideal combination of the following factors:—

(*a*) The total dosage.
(*b*) The method of administration, i.e. the number of injections.
(*c*) The duration of treatment, i.e. the time interval between individual injections.

Bearing in mind the unique property of procaine penicillin with aluminium monostearate of maintaining a steady penicillin level in the blood stream (0.03 unit per c.c. four days after an injection of 300,000 units), it seems as though it may be possible to achieve excellent therapeutic results with a dosage system consisting of two injections of 2 c.c. each week. Optimistic workers are even contemplating giving one injection of 4 c.c. (1,200,000 units) weekly for one or two weeks! There are many changes to ring in experimenting with the time and dosage factors. Many false trails no doubt will be followed. Much good and expensive penicillin will be wasted.

Meanwhile, until the position has been clarified, it is better to adopt a conservative attitude and follow the work of those whose resources and experience enable them to experiment on a large scale. The individual practitioner cannot do this. He is not entitled to draw any worth-while conclusions from the haphazard methods he may employ in a small clientele. Doses of astronomical magnitude are being employed needlessly. For the present, in Cape Town, when aqueous penicillin is used in hospitalized patients suffering from early syphilis we are using, and have used for the past 12 months, a dosage scheme whereby adult patients receive from 40,000 to 60,000 units (depending on body weight) at 3-hourly intervals for 80 injections. This takes 10 days to give and on alternate days they receive an arsenical injection; usually neo-halarsine or maph:rside, in doses conforming to body weight. Bismuth is given twice weekly. On discharge from hospital, a combined course of arsenical and bismuth injections is instituted which lasts for eight to 10 weeks. Thereafter the

patient attends at 3-monthly intervals for two years, if it is possible to hold the case so long. A lumbar puncture is done at the sixth month after treatment. When procaine penicillin in oil is used, the patient attends twice weekly until a dosage equivalent to that used when aqueous penicillin is employed, has been reached; otherwise the treatment scheme is unaltered. Newer schedules of treatment using procaine penicillin oil with aluminium monostearate as a sole curative agent are about to be tried in the Venereal Disease service of Cape Town. Only cases of early syphilis will be subjected to six types of schedules for a six-month period. If clinical trial results in the establishment of a simple method of eliminating early contagious syphilis, a great step forward will have been achieved.

SUMMARY

1. The results obtained in treating 365 cases of early syphilis with a treatment schedule entailing the administration of penicillin, arsenic and bismuth of a 7½-8 day period, are put forward.

2. Only a small number, 86 (23.56%) of the original 365 cases continued to attend for a 12-month period. Of this number 12 (13.95%) were treatment failures.

3. There were no serious reactions observed in any of the patients who were all admitted to hospital for treatment.

4. Seventy-six (20.82%) of the original 365 cases had a complete spinal fluid examination at the sixth month after the completion of treatment. In one of these only was a doubtful reaction observed in the Wassermann tests, all other tests being normal.

5. The schedule tested cannot be regarded as giving very satisfactory results in view of the considerable number of treatment failures in secondary syphilis.

6. The results emphasize once more the favourable outcome in early primary syphilis compared with that obtained in later cases.

I am indebted to Dr. F. O. Fehrsen, Medical Officer of Health, for permission to publish this paper and to Mr. J. M. Swart, Chief Male Technical Assistant and Head Nurse of the Venereal Disease Branch, of the Health Department, City of Cape Town, for the assistance he gave me in abstracting figures from the records.

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RADIOLOGICAL CASE BOOK. XXVII

HYPERAEMIC DECALCIFICATION IN SINUS DISEASE

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X-ray diagnosis of sinus disease is based on:

1. Demonstrable changes in contour and thickness of the lining mucous membrane with or without fluid levels.

2. Changes in the bony walls.

Mucous membrane changes with or without fluid constitute by far the commonest radiological criteria, with bony changes 'the least common demonstrable abnormality' (Young[1]).

Bony wall changes manifest themselves by 'disappearance of the muco-periosteal junction and demineralization of the adjacent bone'.[1]

The muco-periosteal junction (the thin, dense white line at the periphery of the sinus) disappears when infection extends beyond the membrane into the bone. It also disappears when bone is invaded or eroded by new growth.

The accepted cause of demineralization of bone is hyperemia.

The accompanying films are from a case of chronic suppurative pansinusitis with polypi.

This patient gave a history of having had at least nine polypectomies, at 6-9 month intervals, in the preceding 6-8 years. On examination polypi were still present and a large bunch were seen to be occupying the right spheno-ethmoid area and to be bathed in pus.

5 *June*, 1944. Oblique (Rhese) views to demonstrate the ethmoids revealed also that the sphenoidal roof on both sides was radiologically intact. However, films taken two months later (10 August) revealed complete disappearance of the muco-periosteal junction in the vicinity of the sphenoidal roof on both sides.

Two years later (2 July, 1947) this patient revealed complete remineralization of the sphenoid roof on both sides, though nasopharyngoscopically polypi were still present, with the post-nasal space looking, on the whole, cleaner on this occasion.

This patient continued to experience occasional bouts of post-nasal stuffiness and discharge, accompanied at times by severe 'nasal bridge headache'.

When seen again in mid-1949 polypi and pus were again noted nasopharyngoscopically, and on this occasion catheterization of both sphenoid sinuses via their natural openings followed by diagnostic irrigation revealed a considerable quantity of greenish-yellow pus in both.

Both sphenoid sinuses, the site of chronic infection, were apparently subject to periodic exacerbations.

In one of these, radiological confirmation of activity

was shown by roof demineralization. Subsequent abatement was followed by remineralization.

This is analogous to what happens in a whitlow when, during the acute hyperemic stage, the terminal phalanx may become so completely decalcified as to be radiologically invisible, but returns to radiological visibility on subsidence of the infective condition.

The writer wishes to thank Drs. Montgomery, Meyer, Jacobson and van der Merwe, who undertook the radiological investigations.

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LIVER FUNCTION TESTS IN PULMONARY TUBERCULOSIS

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Tuberculous patients do not, as a general rule, show evidence of hepatic dysfunction as judged by clinical methods. The grossly fatty liver and the toxaemia of the tuberculous process suggest that there might be some liver dysfunction which could be shown by the more sensitive and reliable liver function tests.

Aubertin (1922) obtained positive results in marked pulmonary tuberculosis. Steidel and Heise (1933, 1935), using somewhat obsolete tests in all grades of tuberculous disease, found equivocal results in early and advanced stages of the disease. They used the bromsulphalein excretion test in its original form, i.e., the 2 mg. per kilogram of body weight dose. They found no pathological results. Levinson and Siegal (1938), using the same test and the same dosage, found pathological retention of the dye in their cases of pulmonary tuberculosis.

In 1942 Kruger and Gerber, using the more sensitive 5 mg. per kilogram of body weight dose, found impairment of bromsulphalein excretion especially in their cases of far advanced pulmonary disease. Getz *et al.* (1944) studied the nutrition of tuberculous patients and came to the conclusion that the low serum albumin found in their cases of far advanced tuberculosis did not necessarily reflect on the function of the liver.

Maclagan (1946) using one of the newer flocculation tests found only one positive serum colloidal gold test in sera from 18 cases of pulmonary tuberculosis.

Using a battery of liver function tests Hurst *et al.* (1947) found that perhaps only the serial bromsulphalein test gave satisfactory evidence of hepatic dysfunction. Their results were obtained using the 5 mg. per kilogram body weight dose and then only in far advanced cases of the disease.

Kinnear and Keen (1949) using three flocculation tests were unable to obtain satisfactory evidence for liver dysfunction in pulmonary tuberculosis.

MATERIAL AND METHODS

The patients were 27 European and non-European males and females in bed. These patients were kindly grouped into mild, moderate and severe cases of the disease by Dr. J. F. Wicht. The diagnosis in all cases had been made radiologically and bacteriologically. Clinical and radiological examination revealed no evidence of any other disease. Amyloidosis was not found in any of the cases studied. The results from all these cases were pooled for statistical analysis where appropriate.

Total serum proteins were determined with the biuret reagent of Weichselbaum (1946). The colour evolved was read in a Hilger photo-electric absorptiometer which had been calibrated by triplicate macro Kjeldahl determinations. A filter having maximum transmittance at 555 μ. was used. As 28% sodium sulphite precipitation of globulins parallels more closely the electrophoretic pattern, it was used in preference to the older Howe method using sodium sulphate. The precipitated globulin was packed in the centrifuge utilizing a Tween 80-ether mixture as suggested by Wolfsohn *et al.* (1948). Both the above estimations were run in duplicate and results differing by more than 0.2 gm. were discarded.

Gamma globulins were precipitated with 1.93 M. ammonium sulphate as in the method of Wolfsohn *et al.* The colour evolved with Weichselbaum's reagent was read in the absorptiometer as for serum proteins.

Serum bilirubin was estimated after the method of Malloy and Evelyn (1937) using an Evelyn photo-electric colorimeter and filter 540.

The intravenous hippuric acid test was run with the refinements in technique suggested by Weichselbaum and Probstein (1939). The technique used was essentially that of Londe and Probstein (1941) in which an excess of concentrated hydrochloric acid was found an advantage. The ranges of normality used were those of Scurry and Fields (1943).

Bromsulphalein excretion was measured in the Evelyn photo-electric colorimeter after the method of Gaebler (1945) which allows one to treat turbidity, alkaline haematin and bilirubin as one interfering substance. For the instrument in the author's laboratory bromsulphalein in mg. per 100 c.c. was calculated from the formula:

$$\frac{L565 - 0.004}{0.1174}$$

The dose used was 5 mg. per kilogram of body weight as first suggested by MacDonald (1939). A 45-minute interval was used.

The thymol turbidity test was performed using the thymol buffer of Maclagan (1946) and the readings made in the Evelyn photo-electric colorimeter calibrated with copper sulphate and using the red filter at 660 μ. after the method of Ducci (1947). After the thymol turbidity had been read a portion of the solution was placed in a small test tube and left undisturbed overnight. Flocculation was graded 0− 3+ the following morning.

The serum colloidal gold test was run using the modified gold sol of Maclagan (1948) and a buffer at pH 7.7−7.8.

A modified cephalin cholesterol flocculation test of Hanger (1939, 1941) was used utilizing both cephalin prepared in this laboratory and the Difco product. No significant difference was found between the two antigens. Serum, as emphasized by Neefe (1946), was kept out of the light as much as possible. Non-specific results were minimized by using alkalinized saline as suggested by Krautmann (1946). In addition, positive and negative sera were run with each batch of tests as saline controls were found to be utterley unreliable.

Urobilinogen was tested for with the modified reagent of Watson (1944) and the results recorded as normal to 4+.

The urine of all cases was carefully analysed and those few cases showing proteinuria had a van Slyke's urea clearance test done before injection of sodium benzoate for the hippuric acid test.

RESULTS

The results obtained in this survey are set out in Table I. Under each heading the first line enumerates the results which fall within generally accepted normal limits. The next line or lines indicates degrees of abnormality as set out on the left.

Ten mild cases, nine moderate cases and eight gross cases of pulmonary tuberculosis have been studied.

Table II shows the statistical values.

FLOCCULATION TESTS

Thymol Turbidity test. Positivity of the thymol turbidity test is probably associated with an excess of gamma globulin in the particular serum. Albumin has an inhibitory effect on the precipitating action of the thymol reagent while the relation of the test to the total globulin content of serum is somewhat doubtful. The beta globulins have been involved in the mechanism of the test. Cohen and Thompson (1947) and Kunkel and Hoagland (1947) demonstrated a fall in the beta globulin content of serum after treatment with the thymol reagent. Isolated beta globulin does not, how-

ever, react with the thymol reagent. Phospholipid, on the other hand, is probably essential to the positive thymol reaction. Maclagan (1948) suggests that as phospholipid is mainly associated with the beta globulins, it is the extraction of this phospholipid for interaction in the thymol test that might well explain the decrease in the beta globulin peak of the electrophoretic pattern.

TABLE I

	Mild Tuberculosis	*Moderate Tuberculosis*	*Advanced Tuberculosis*
Thymol Turbidity Test			
*0 *to* 4 *Maclagan units* ..	10	8	2
5 *to* 9 *Maclagan units* ..	—	1	6
Thymol Flocculation Test			
*0 *to* + ...	10	9	7
++ *to* +++	—	—	1
Serum Colloidal Gold			
*0 *to* 2	8	5	0
3 *to* 5	2	4	8
Cephalin Cholesterol Flocculation			
*0 *to* ++	10	8	3
+++ *to* ++++ ..	—	1	5
Total Serum Proteins (%)			
*6 *to* 8	10	7	2
More than 8	—	2	6
Less than 6	—	—	—
Serum Albumin (%)			
*3·6 *to* 5	10	5	2
Less than 3·6	—	4	6
Serum Globulin (%)			
*1·3 *to* 3·2	5	2	0
3·3 *to* 5·0	5	7	8
Serum Gamma Globulins (%)			
*0·66 *to* 1·3	2	2	0
Over 1·3	8	7	8
Intravenous Hippuric Acid (*gm. Sodium Benzoate*)			
*0·80 *to* 1·38	10	9	6
Below 0·80	—	—	2
Bromsulphalein Excretion (*mg. per* 100 *ml.*)			
*0 *to* 2	5	3	0
Over 2	5	6	8
Serum Bilirubin (*mg. per* 100 *ml.*)			
*0 *to* 0·8	8	8	5
Over 0·8	2	1	3
Urobilinogen			
**Normal to* + ...	10	8	7
++ *to* ++++	—	1	1

**These values indicate the normal range.*

TABLE II

	Range	Mean	Standard Deviation	Standard Deviation ofthe Mean
Total Proteins (%).	6·8 – 8·5	7·7	0·49	0·10
Serum Albumin (%).	2·5 – 4·8	3·9	0·66	0·13
Serum Globulin (%).	2·0 – 4·7	3·8	0·69	0·14
Serum Gamma Globulins (%).	1·1 – 2·1	1·55	0·30	0·06
Serum Bilirubin (mg. per 100 ml.)	0 – 1·58	0·45	0·45	0·09
Intravenous Hippuric Acid (Gm. Sodium Benzoate).	0·53 – 1·32	0·94	0·18	0·04
Bromsulphalein Excretion (mg. per 100 ml.)	1 – 8	3·7	1·9	0·4

Of the 27 patients tested seven showed a positive thymol turbidity test. Of these seven cases six were in the advanced stage of the disease, while one case was from the group termed moderate. They showed in addition abnormal values for total globulin and gamma globulin. In six of these cases the albumin level was below 3.6%.

Parallel runs of total serum lipoids on these cases were within normal limits.

Thymol Flocculation Test. Of the 27 patients tested 26 showed at most a one-plus result. Only one case showed what might be construed as a +++ result. This was a case of gross bilateral disease of the lungs. The author has not met with a ++++ flocculation in this test even in the presence of gross hepatitis which showed grossly abnormal results with other liver function tests.

Serum Colloidal Gold Test. The protein fraction responsible for positivity of this test is probably the same as that in the thymol turbidity test. Differences in sensitivity in batches of gold sol prepared by various methods have perhaps led to conflicting reports with this test. However, the citrate sol and buffer suggested by Maclagan are eminently satisfactory.

Kinnear and Keen (1949) demonstrated 11 abnormal gold values in a series of 38 patients tested. Maclagan (1946) showed one positive colloidal gold test in a group of 18 tuberculotic cases; the severity of the disease in his 18 cases is, however, not stated.

In the present series 14 abnormal gold tests were demonstrated in a total of 27 patients. Of the eight grave cases of the disease all gave a positive reading. In addition four of the moderate cases and two of the mild cases of the disease showed positive results.

The gold test is known to give a fair percentage of positive results in such conditions as heart failure, glandular fever, subacute infective endocarditis and rheumatoid arthritis.

Cephalin Cholesterol Flocculation. The precipitating agency in this test is a negatively charged solution of cephalin-cholesterol, but it would appear that the reaction here, as in the colloidal gold reaction, is not one of mutual charge neutralization as in the pH range 7.7 to 8.6 all proteins carry a negative charge. It is probably, as Maclagan suggests, one in which intrinsic differences in protein structure play their part. The function of the alpha aind beta globulins in this test is not quite beyond dispute, while as before the albumin appears to have an inhibitory effect on the precipitation.

In the present series only six of the cases showed an abnormal cephalin cholesterol test. Of these six cases five were grave cases of the disease while the sixth was from the group termed moderate. It is noteworthy that these six patient showed abnormal thymol and gold tests as well, while three patients in the advanced stage of the disease showed negative cephalin tests but positive gold and thymol tests. These six cases showed,

too, abnormal globulin and gamma globulin values associated in five cases with a low serum albumin and, in one case, with a normal albumin.

In general, these tests are of obvious value in diseases not primarily infective. The answer in infective hepatitis is obvious. These tests generally depend on a relative excess of gamma globulin for their positivity. In infective disease, if there is any considerable rise in antibody titre, a rise in the gamma globulin fraction is generally expected. Thus the interpretation of these tests as hepatic function tests in these infective conditions must be viewed with some caution.

It is interesting to note the experiences of Strade *et al.* (1949) with the colloidal scharlach red test of Maizels (1946). These authors conclude that the scharlach red test is a reliable index of antibody formation and does not owe its positivity merely to an excess of non-specific gamma globulin. Work on this hypothesis is at present in hand and will be reported shortly.

Albumin generally has an inhibitory action on the precipitating effect of the gamma globulins but even here differences in action have been noted. It has been shown that albumin separated from normal controls would inhibit the thymol reaction while albumin isolated from hepatitis serum did not have this protective effect. Similarly Maclagan and Bunn (1947) found that gamma globulin separated from hepatitis serum produced flocculation with the thymol reagent whereas normal gamma globulin gave a turbidity but no flocculation. They, too, showed that alpha and beta globulins isolated from hepatitis serum precipitated the cephalin reagent whereas normal alpha and beta globulins did not. Similar differences were found for the cephalin cholesterol test by Moore *et al.* (1945) and Guttman *et al.* (1947).

TOTAL SERUM PROTEINS

The bulk of the patients showed values within the generally accepted normal limits. Eight patients, however, had total protein values in excess of 8%. This elevation was not a marked one as the highest value obtained was 8.5% and the lowest figure above the accepted normal of 8% was 8.2%.

For all the values the mean was 7.7% with a standard deviation of 0.49% and a standard deviation of the mean of 0.10. These figures are not significant.

SERUM ALBUMIN

Of the total of 27 patients only 10 showed an albumin level below 3.6%. Of these 10 patients, six were gross cases and four were moderate cases of the disease. The relation of albumin to the empirical liver function tests has already been discussed. The mean for all cases was 3.9% with a standard deviation of 0.44% and a standard deviation of the mean of 0.10.

SERUM GLOBULIN

Twenty-one patients of the total of 27 showed globulin values above the accepted normal of 3.2%. This is an expected finding if, as Kunkel (1947) suggests, every case of hyperglobulinaemia is probably due to a general increase in the gamma globulin fraction of the serum, and antibody formation is closely linked with the gamma globulin fraction. This has been found in this series of cases but does not tally with the series reported by Hurst *et al.* (1947) in which 12 cases of advanced disease showed globulin values ranging from 2.03-3.65% with only three cases showing values above 3.2%.

The mean in the present series was 3.8% with a standard deviation of 0.66 and a standard deviation of the mean of 0.14.

GAMMA GLOBULINS

If 0.66-1.3% is accepted as an average normal range then 23 patients out of 27 showed an elevated gamma globulin value. This is an expected finding as indicated above and its relation to the flocculation tests and serum albumin has been discussed. The mean over the whole series was 1.55% with a standard deviation of 0.30 and a standard deviation of the mean of 0.06.

The relation of antibody globulin to the scharlach red test has been discussed above.

INTRAVENOUS HIPPURIC ACID

Hurst *et al.* found no impairment of hepatic function using this test. Two of the present series of advanced cases showed figures below 0.80 gm. hippuric acid as sodium benzoate. These two cases showed abnormal flocculation, abnormal bromsulphalein and hyperglobulinaemia. Elevated gamma globulins and reduced albumin values were found but bilirubin and urobilinogen levels were within normal limits.

Table II shows that statistically the results are not significant.

BROMSULPHALEIN RETENTION

Abnormal retention of dye is to some extent related to the activity of the Kupffer cells of the reticulo-endothelial system. It is known, too, that the dye disappears from the blood stream of normal animals faster than it is excreted in the bile. Some hold that there is destruction of the dye in tissues to account for this observation. The 5 mg. per kilogram of body weight dose has been said to be the more sensitive test as it throws a greater strain on the liver cells. Mateer *et al.* (1943), after a comprehensive study of the problem, decided: 'The 45-minute period has been adopted therefore as the normal standard for complete disappearance of the dye after injection of 5 mg. of bromsulphalein per kg.'

If one uses this rather stringent base line then in the present series 25 out of the 27 cases gave abnormal results. If, however, one uses a normal range of 0-2 mg. per 100 ml., especially when sensitive photo-electric methods of analysis are used instead of the grosser visual methods, then 19 cases showed abnormal results. Of these 19 cases five were derived from the group termed mild tuberculosis, while six of the eight cases of the moderately advanced disease showed abnormal retention of the dye. All eight cases of the advanced disease showed pathological retention of the dye.

The statistical figures are shown in Table II.

SERUM BILIRUBIN

The upper limits of normal vary within fairly wide limits as reported by various authors. Harrison (1947) gives the range 0.10-0.5 mg. per 100 ml. Lichtman (1942) gives the upper limit of normal as 0.5 mg. per 100 ml., while Cantarow and Trumper (1945) give the upper limit of normal as 0.8 mg. per 100 ml. The upper limit has been arbitrarily set at 0.8 mg. per 100 ml. for the present series.

In this series the range was from 0-1.57 mg. per 100 ml. with a mean value of 0.45 mg. per 100 ml. and a standard deviation of 0.45. The standard deviation of the mean was 0.09. The mild group of tuberculotics showed values above 0.8 mg. per 100 ml. in two cases, while the moderate and advanced groups showed one and three abnormal values respectively. The value of 1.57 mg. per 100 ml. was obtained in one case which was, clinically at least, not as far advanced as the other grave cases of the disease studied.

Statistical evaluation shows no significant results.

UROBILINOGEN

It has been stated that one of the most sensitive tests of liver cell damage is the urinary urobilinogen excretion. Hurst *et al.* found normal figures for their series of advanced tuberculosis. The qualitative test gave only two positive results in the 27 patients tested.

COMMENT

In all hepatic function studies the tremendous reserve power of the liver must always be remembered. In dogs four-fifths of the liver may be removed surgically without gross threat to life. The functions of the liver are many and no single liver function test designed to test one function can be relied upon to give information about the liver as a whole.

A whole battery of tests has been devised, in itself an admission of the unsuitability of any one test. At present these tests will have to be applied if accurate information is to be gained about some of the functions of the liver. In fact, it has been said that the best liver function tests are carefully taken histories, thorough physical examinations and competent analysis of urine.

From the present series it would appear that severe tuberculosis is associated with hepatic dysfunction, at least as shown by the current liver function tests. The best correlation has been shown by the cephalin cholesterol test, the bromsulphalein retention test and the thymol turbidity test.

SUMMARY

1. A battery of liver function tests was run on 27 tuberculous patients grouped into severe, moderate and mild categories.

2. Hepatic dysfunction was found in a large proportion of the cases of severe pulmonary tuberculosis studied.

3. The best correlation was found between the thymol turbidity test, the cephalin cholesterol flocculation test and the bromsulphalein excretion test using the 5 mg. per kilogram of body weight dose.

4. Statistical analysis of the overall results show no significant figures.

The author expresses his gratitude to Prof. R. Turner for encouragement during the course of the work and for permission to publish this paper.

The patients were under the care of Dr. J. F. Wicht, Director of Hospitals and Dr. H. F. Ackermann, Deputy Director of Hospitals.

Much of the intravenous work and collection of specimens was meticulously carried out by Dr. E. Movsovic.

The author wishes to thank Mr. F. M. Rae for valuable technical assistance.

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VERENIGINGSNUUS : ASSOCIATION NEWS

KINGWILLIAMSTOWN DIVISION: ANNUAL DINNER, 25 NOVEMBER 1949

DR. A. W. BURTON'S REPLY TO THE TOAST OF *The Medical Association of South Africa* PROPOSED BY DR. JOHNSTON

I am deeply grateful for your invitation and for the honour and privilege of responding on behalf of the Association. It is often easier to propose than to reply to a toast and bridegrooms will, I know, uphold me in that respect. It may be, gentlemen, that you have conferred this honour upon me in appreciation of my past services on behalf of the Association in which I have always been interested and I thank you more sincerely if that be so. That, to some extent, makes the reply a personal one; but I would prefer to place the interests of our profession and our Association first and my personal efforts last on such an occasion as this. As memory is apt to recede with advancing age you will, I know, pardon my reading this reply which may not be without interest coming, as it does, from an ordinary general practitioner who has been through the mill and witnessed many changes both at home and abroad.

Ours is a profession closely related to many branches of Science. A doctor starts his career with an academic education embracing the Classics, Botany, Zoology, Chemistry and Physics. Nature is to a great extent the background: then follows that long series of subjects too numerous to mention here. But in all our long training which keeps pace with the advance of Science the power of Nature is never lost sight of—we still believe firmly in the *vis medicatrix naturae* to which the founders of Medicine, hundreds of years before the Christian era pinned their faith. We also cling to the belief that without the 'milk of human kindness' as an essential form of sustenance we can never succeed in winning the esteem and gratitude of suffering humanity as the best reward of our labour and of the trust and confidence placed in us.

Before the Christian era the foundations of Medicine were laid in ancient Greece, but in those early days our art was associated far more closely with philosophy than it is today. If we review the writings, works and teachings of Pythagoras, Hippocrates, Aristotle, Socrates, Plato, and even of the historian Herodotus, we realize that fact and wonder if there is really anything new under the sun. The works of Aristotle on maternity practice are still worth reading, in spite of the fact that he was one of the greatest of Greek philosophers. To the credit of the ancient Greeks it must be admitted that for them *Question* was more important than *Answer*. That attitude alone showed their acute and quick intelligence for trying to see things as they were and for seeking a rational explanation of human maladies and of the universe.

Today the world has been staggered by the splitting of the atom; but even our conception of modern physics is based on the theory propounded by Leucippus—the Greek scientist who almost half a century before Christ held that the world was made up of atoms combined in an infinite void.

The ancient Greeks tried to rise above a world then dominated by superstitions and traditional beliefs. It was long before the Christian era that Pythagoras became the founder of scientific Medicine and Hippocrates the greatest doctor of the age who was a native of Thessaly and practised in Athens; but Hippocrates himself was bound by traditions, beliefs and customs. He was unable to free himself from the trammels of superstition for he used human bones as medicine. His dictum was, 'the dead when converted into medicine will expel human maladies and ashes prevail against ashes'. In other words, human dust was a panacea not only for illness—it had other potencies among a people who believed in the transmigration of souls. The dust of a good and clever man was valued highly as a medicine. Furthermore, Hippocrates used drugs and violent remedies as little as possible, leaving the curative powers of nature to assert themselves.

Not long ago there came into my possession a document which proves that these beliefs were held at Lewes in the county of Sussex, England, in 1613, 2,000 years after the death of Hippocrates.

Near our own doors to-day, and in Basutoland, we hear and read of witch doctors rifling graves and committing ritual murders. To my mind there is some definite link between the practice of the ancient Greeks and the witchcraft of South Africa as we have learned to know and yet fail to understand it.

South Africa to-day is taking an increasing interest in the Bantu and it is perhaps not generally remembered that ethnologically, the Bantu were related to the ancient Greeks. The Bantu were not always what they are to-day. They are a people who, during the ages, wandered over the African continent and fell from higher to lower estate. Their customs of to-day (I can name 12 at least) connect them with the Bavili people in the North and those people were Bantu among whom there were great and distinguished personages. Among such were: Thales, the father of Greek philosophy (625 B.C.)—one of the seven wise men of ancient Greece; Hannibal, the greatest general of antiquity, also B.C.; Cadmus, 1550 B.C., founder of Thebes ancient capital of Egypt. He introduced the alphabet into Greece; The Phoenicians, ancient traders of the world, were a branch of the Canaanites who founded the colony Carthage. These were all related to the Bantus. The word 'Bantu' means nothing more than a person and among the thousands of milestones between Athens the home of our founder and our own homes there are many which we could not justifiably paint white. They belong to the descendants of Ham, many of whom are, to-day, struggling to rise from their fallen estate. The ethnological key to all this is the sons of Noah—Shem, Ham and Japheth.

The ancient world went on: nations and empires rose and perished. The spirit of ancient Greece permeated the Roman Empire which after a thousand years gave way to the great Renaissance of the 15th and 16th centuries when the art, literature, science and philosophy of ancient Greece came into its own again and the West prevailed over the East as western civilization evolved.

But to-day western civilization is on trial after two world wars. The shadow of a new civilization is spreading over the world and even over our own country and it would seem that out of some form of compromise between east and west, a modified civilization is peeping out of world chaos and disorder. But our destiny is not something to be awaited—it is something to be achieved through correct and just human relationships, freedom of the human spirit and justice.

Time has antiquated the scientific achievements of ancient Greece. As far as we ourselves are concerned the arts of prescribing and dispensing have become simplified and modern remedies are in many instances more rapid in action and more efficacious. Most of these are indispensable in spite of their increasing costs. The public press for 'blitz treatments' and are indulging in 'ramps' or 'rackets' embracing the vitamins which common foodstuffs can supply in their natural form as nature intended should be the case.

Blotting-paper prescribing has knocked the bottom out of the art of dispensing and the knowledge of pharmacology—the shop-rounds and carboys of the pharmacist with the bold, mysterious and glittering impressions of former years are consigned to the back of the premises and many pharmacies are now drug-stores tidy and neat like the best of grocers' shops.

Galenicals and other proprietary remedies with fanciful names are crowded on the shelves and many soon become quite unsaleable and dead stock. By and large things have become easier for the doctor but far more difficult for the pharmacist whose need of a pharmacopoeia is gradually vanishing.

So it goes with Medicine and its related sister Pharmacy; but the literature and the philosophy of Homer, Plato, Aristotle and other ancient Greeks are living and instructive to-day. If the ancient Greeks had not existed the philosophy and science of the west would never have evolved as it did. There is little or nothing in our intellectual life which has not sprung from seeds sown in ancient Greece; but that country to-day is torn asunder by civil warfare. The statesmen of the world continue to shear the sheep and the politicians delight in skinning them. We have however a few links with the past—'Academy' was the name of Plato's house; 'Museum' or 'Temple of the Muses' founded by

Ptolemy, father of libraries and universities, is still a household word with us. The torcular Herophili with which you are all acquainted and the tendo Achillis made famous by Homer in his *Iliad* are a few examples.

What we call progress seems to be the exchange of one nuisance after another, but in any case the woman of to-day must be a different woman from her grandmother and he who has not the spirit of his age, has all the misery of it.

Macbeth was not far wrong when he said:

'To-morrow, and to-morrow, and to-morrow,
Creeps on this petty pace from day to day.'

If the progress of science is to be assured there must be—A desire to know; rational explanation for phenomena; open-mindedness and candour; industry and observation.

Medical Associations Locally and Personally

As a final-year student I joined the B.M.A. in Edinburgh in 1909. I sometimes wonder whether final-year students in our medical schools have that privilege in respect of the M.A.S.A. If not, it might be to their good.

Having qualified a year later it was my privilege to read two papers before the Edinburgh branch in 1910. When I settled in Kingwilliamstown in 1911 there was no form of medical association. Fees were 5s. and 2s. for friendly societies, both any hour of the day or night. The performance of a major operation at our hospital was a risky undertaking bordering on disaster, for there was no dry sterilization plant and the theatre looked more like a kitchen with its blinds, linoleum and a multiplicity of pots, pans and fish kettles, all of which have long since disappeared.

In 1919 the late Dr. Ben Blaine suggested that a Kingwilliamstown Medical Practitioners Society should be formed. I moved for a division of the B.M.A., as there was nominally more than actually a branch at East London. We formed a Division of which I became Secretary. I never became chairman, I think for the reason that the secretary was regarded as the leader or backbone of the association and I was the willing horse for very many years.

Later I became President of the Border Branch and was a member of the Federal Council and present at the meeting in Johannesburg when it was decided to change our name and to remain affiliated to the B.M.A. overseas on a basis of friendly relationships.

In 1935 I was, to my great surprise, the recipient of the Hamilton Maynard Memorial Medal for 1934 and I wear the medal this evening as I am supposed to do on occasions such as this. The honour, as you know, is awarded annually by the Head Office and Journal Committee for the best paper contributed during each year.

In 1938 I visited the Head Office of the B.M.A. in Tavistock Square, London, and lodged a protest on behalf of South African doctors on the question of reciprocity between ourselves and continental doctors. If we desired to practise on the continent we were compelled to take a full six-year medical course in a continental university while continental doctors were being let loose upon us after a brief period of work—12 months and the lowest diploma in the British Isles known as the L.S.A. or Licentiate of the Society of Apothecaries entitled them to practise in Great Britain and the Colonies. I kicked up a 'shindy' and the B.M.A. Secretary asked me to come down to Plymouth with him and to address the B.M.A. there in order to obtain redress of our grievance over which you need have no worry nowadays. I did not go. I bought a car and took to the roads through the Highlands of Scotland, which were far more pleasing to me. I left the matter to the Secretary. You and your sons now have a large measure of protection against that gross injustice.

Before I close I would like to place some emphasis upon the value of our affiliation with the B.M.A. from which we sprung and have our being. From the B.M.A. we received much support and guidance in the setting-up of the M.A.S.A. and those who go overseas have much to gain through the spirit of friendliness and co-operation. We are, after all, a young, rapidly progressing country but our rate of progress must for some considerable time to come remain checked or limited.

Finally I would advise each of you to cultivate a hobby of some kind—something that may be brought into play when younger colleagues take your places and time is apt to drag you down and life tends to become rather boring. Even an intellectual hobby can please one not inclined to any form of manual labour or outdoor games. Choose your own way and type of hobby before retiring: then life will not prove lonely. I have followed Herodotus and Limnaeus in history and natural history, both dry enough subjects but nevertheless interesting in their own spheres and not without their own rewards for the former brought me a great honour in 1943 when awarded the medal of the Historical Monuments Commission.

On behalf of both the M.A.S.A. and the B.M.A. I thank you for honouring the toast proposed by my old friend Dr. Johnston. Continue striving in faith, hope and charity, ever bearing in mind that good fellowship and charity towards the public and next towards each other in all your work can alone ensure your happiness and success in the ranks of our noble profession. In the coming great changes in hospitalization I sincerely trust that any changes in the nature of your work and welfare will prove satisfactory in every respect in the changing world of to-day.

IN MEMORIAM

DR. ANDREW G. BESTER

The sudden death of Dr. Andrew G. Bester at Port Elizabeth came as a great shock to his wide circle of friends and acquaintances. Since his setting up practice in Port Elizabeth, he became well known to many residents both for his qualities as a man and capabilities as a doctor.

After a brilliant career at the Paarl Gymnasium High School he decided to make medicine his life's work and follow in the footsteps of his uncle who is still active. He graduated M.B., Ch.B. at the University of Cape Town in 1927. After graduation he did various locums in Kenhardt, Bloemfontein, Durban and Kokstad, where he met his wife. Then he settled at Umtata where he practised for seven years, and in 1936 he went overseas and took his F.R.C.S. at the University of Edinburgh. Returning to South Africa, he set up practice at Port Elizabeth as a general practitioner with a special leaning towards surgery and just before his death decided to make surgery his speciality.

His sudden death has caused a great blank in the close relationship with his fellow practitioners.

He was a keen sportsman and was especially good at hunting and fishing. He leaves a widow with whom we all share in her great sorrow.

F.P.B.

PASSING EVENTS

Dr. Francis William Roberts, M.B., B.S. (Lond.), F.F.A.R.C.S., D.A., (R.C.P. & S.), formerly Honorary Anaesthetist, The Middlesex Hospital, London, Conservator in de Narkoseleer, Rijksuniversiteit, Utrecht, Holland, and lately Principal Anaesthetist, Johannesburg Hospital, has commenced practice as a specialist anaesthetist in partnership with Dr. Cyril Frost at 211 Lister Building, Jeppe Street, Johannesburg. Telephone: *Rooms*, 22-1538; *Residence*, 42-6385.

POST-GRADUATE MEDICAL LECTURES: DR. FOURACRE BARNS

Members are advised that these lectures will now be held on Tuesday, 28 February 1950 (*Diabetes and Pregnancy*) and Tuesday, 7 March 1950 (*Stress Incontinence*).

The lectures will be delivered in the Physiology Lecture Theatre at the Medical School, Mowbray, C.P., at 8.15 p.m.

* * * *

Dr. Alexander Brown, F.R.C.S. (Eng.), has recently returned from overseas where he was Surgical Registrar at St. Mark's Hospital, London.

He has begun practice as a surgeon at 526 Groote Kerke Buildings, Parliament Street, Cape Town. Telephone 2-1403.

* * * *

Those colleagues who attended the dinner in honour of Dr. Frank Bester of Paarl on 13 January 1950, may wish to have

a memento of the occasion in the form of one of the photographs taken on that occasion. A group photograph is available and can be obtained from the photographer: Mr. Henri Kreuger, P.O. Box 18, Paarl. The price is 6s. 6d. each.

S.A. Society of Obstetricians and Gynaecologists

The South African Society of Obstetricians and Gynaecologists is to hold a meeting of its members in Durban from 30 June to 3 July, at which papers will be read and discussed. The Honorary Secretary of the Society is Dr. Bryan Murless of 807-8 Acutt's Arcade, Durban.

Medical Aid Society Tariff Books

Many members seem to be under the impression that the Medical Aid Societies have their own tariffs and tariff books. This is not so. The Tariff of Fees for Approved Medical Aid Societies is published only by the Medical Association of South Africa. When this tariff first appeared, copies were supplied to all members. Additional copies may be obtained from the Association's Head Office, P.O. Box 643, Cape Town, at a price of 7d. per copy post free.

NEW PREPARATIONS AND APPLIANCES

Cliftol (Concentrated Lacto-Protein Extract)

Cliftol fulfils the need for a biologically-complete protein which is soluble in water, orally administered, and without the unpleasant flavour associated with many protein concentrates. Thus it can be used to replace the high protein loss occasioned by illness, trauma, operation or childbirth in a way which is acceptable to the patient.

Clinical experience is also being accumulated concerning the importance of high protein diets in the treatment of amoebic dysentery, peptic ulcer, pancreatic disturbances and kidney complaints. In cases of malnutrition it is already clearly recognized.

Prepared from milk in the form of a tasteless white powder, Cliftol offers the medical practitioner an 85 per cent. protein concentrate, containing all the amino acids in the molecule. A regime of protein hyperalimentation, using Cliftol, is now being instituted in many leading hospitals and nursing homes.

One ounce of Cliftol is equal in protein content to approximately three glasses of milk or 4 ozs. of meat.

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Where it is required for institutions, clinics, feeding schemes, and for dispensing practices (especially those catering for non-European patients) bulk packings in 10 lb. tins or 55 lb. drums are obtainable at special prices.

Cliftol is made by New Clifton Manufacturers (Pty.) Ltd., Industria, Johannesburg.

Distributors: Selected Pharmaceuticals (Pty.) Ltd., P.O. Box 5785, Johannesburg.

BOOK REVIEW

Syphilis : Its Management

Syphilis: Its Course and Management. By Evan W. Thomas, M.D. (Pp. 317 + xix. With 68 illustrations. 42s.) London: Macmillan and Company, Limited. 1949.

Contents. 1. Etiology of Syphilis. 2. A General Description of the Course of Untreated Syphilis. 3. Immunology of Syphilis. 4. Interpretation of Quantitative Serologic Tests for Syphilis (Sts). 5. Iodides, Bismuth, Arsenicals, and Fever Theraphy. 6. Antibiotics in the Treatment of Syphilis. 7. Principles Underlying Antisyphiltic Treatment. 8. The Examination and Education of the Patient. 9. The Diagnosis and Treatment of Early Infectious Syphilis. 10. Latent Syphilis. 11. Late Benign Syphilis. 12. Cardiovascular Syphilis. 13. Neurosyphilis. 14. Syphilis and Pregnancy. 15. Congenital Syphilis. 16. The Public Health Aspects of Syphilis.

This volume contains many new ideas. It is the most complete evaluation of the treatment of syphilis with penicillin that has yet appeared.

The author, who is the Director of the Rapid Treatment Center at the Bellevue Hospital, New York, bases his results and ideas on the experience obtained by treating 12,000 cases of syphilis in the Bellevue Hospital.

Great emphasis is placed on the value of quantitative serological tests in the control of treatment.

The author's dissatisfactions with the results obtained with 'routine' therapy with arsenic and bismuth (courses of nine to 18 months) are readily understood when he states that less than 20% of his clinic patients completed this type of treatment.

Rapid treatment with fever and mapharside was dangerous.

He has little use for mercury, iodides or tryparsamide. Phenarsine (mapharside) is used. Of bismuths, he favours the subsalicylates in oil. Fever is employed when other methods are unsuccessful. The results obtained in early syphilis with various schedules of penicillin, either given alone or combined with arsenic and bismuth, are set out. The various preparations of penicillin are compared. Bacitracin is mentioned but aureomycin is not.

He believes that the persistence of low reagin titres for many months after the treatment of early syphilis does not mean the continued presence of foci of infection. He strongly advises monthly blood tests during the first year, two- or three-monthly during the second year and yearly thereafter.

There is a final chapter on the *Public Health Aspect of Syphilis* by Theodore J. Bauer, Chief of the Venereal Diseases Division of the United States Public Health Services, with interesting statistics.

This is not a textbook of clinical syphilis. The only illustrations are graphs and a few reproductions of X-rays.

The book is whole-heartedly recommended to all interested in the treatment of syphilis. It is attractively printed and bound and is a fresh and valuable addition to the literature on the subject.

CORRESPONDENCE

The Mrs. Coppinger Appreciation Fund

To the Editor: I would like to take the opportunity of thanking, through the columns of the *Journal*, all those members of the Medical Association who contributed so generously to the Mrs. Coppinger Appreciation Fund.

It is difficult for me to express in words the deep sense of appreciation I have of the kindness shown by so many of the doctors with whom I have been associated for so long.

I shall miss the work very much and I would like to express my best wishes for the future of the Association.

'Athlone',
Uvongo Beach,
South Coast, Natal.
30 January 1950.

Mrs. Wm. Coppinger.